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by Gertjan J.L. Kaspers

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Prime salvage treatment for pediatric acute myeloid leukemia

Gertjan J.L. Kaspers[1,2,3]

Affiliations

1. Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands
2. Emma Children's Hospital, Amsterdam AMC, Vrije Universiteit Amsterdam, the Netherlands
3. Ghent University, Department Internal Medicine & Pediatrics (GE35), Belgium

Correspondence

Prof.dr. Gertjan J.L. Kaspers - gjl.kaspers@amsterdamumc.nl

Disclosures

None

In this issue of Haematologica, Fan et al. report relatively favorable outcomes of children with refractory or relapsed acute myeloid leukemia (R/R AML), using priming with decitabine followed by the combination of low-dose cytarabine subcutaneously, low-dose idarubicin and G-CSF (DP-IAG).[1] In 101 children, the majority having refractory disease, 73% achieved a complete remission (CR) with or without hematologic count recovery, and 3-year probability of overall survival (pOS) was 61%. This indeed compares favorably with the largest and only randomized study reported sofar in pediatric R/R AML, in which the best arm (fludarabine and cytarabine (FLA) plus G-CSF and liposomal daunorubicin) resulted in a CR rate of 69% and a 4-year pOS of 40%.[2] There are no prospective, large studies that report equally good outcomes overall as shown by Fan et al., as reviewed recently.[3] Yet, it is too early to conclude that this regimen using priming with decitabine, chemosensitization with G-CSF and low-dose idarubicin and cytarabine is the new standard-of-care regimen in pediatric R/R AML. That would require a larger, randomized study. Also knowing that 30 out of the 101 patients received targeted therapy (sorafenib or dasatinib) in addition to DP-IAG.

By and large, most pediatric AML experts would agree that FLA plus or minus an anthracycline or gemtuzumab ozogamicin is the standard-of-care for salvage or reinduction chemotherapy in case of refractory or relapsed disease, respectively.[4,5] However, since neither remission rates nor survival rates with that approach are satisfactory, we do need clinical trials exploring other regimen. Randomized trials are possible through international collaboration, and using measurable residual disease as early surrogate endpoint, thereby reducing the numbers needed to prove that a new regimen is better.[6] Certainly, the DP-IAG regimen should be one of the regimen to be investigated. Epigenetic priming resulting in lower genome-wide methylation is an interesting concept, that was also tested in the US multicenter AML16 trial. At the 2025 ASH meeting, data were presented on 200 children with newly diagnosed AML, showing the safety of priming with either decitabine or azacytidine and suggesting better outcomes than previous trials, albeit it historical comparisons.[7] Of interest, decitabine appeared superior to azacytidine.

Another approach that is promising and potentially effective in the majority of patients, is the combination of chemotherapy with a bcl2-inhibitor as chemosensitizer by enabling drug-induced apoptosis.[5] Especially venetoclax is frequently used in children and well tolerated, while the majority of children with AML have leukemic cells expressing bcl2. Therefore, we also need a larger, randomized study on any chemotherapy regimen plus or minus venetoclax. In fact, such a trial is ongoing in R/R AML, the so-called ICC-101/APAL2020D (NCT05183035).

In addition to novel, broadly applicable regimen mentioned above, more and more targeted treatment options become available.[5] Obvious examples already being or soon to be studied in pediatric AML include flt3-inhibitors such as sorafenib, gilteritinib and quizartinib, and menin-inhibitors such as revumenib and bleximenib. Flt3-inhibitors already demonstrated improved survival in randomized trials in adults with AML when combined with chemotherapy and as continuation treatment post-transplant. The COG group reported on the safety and efficacy of sorafenib in children with AML and a FLT3-ITD, results showing improved outcome as compared with patients not getting sorafenib.[8] The COG is currently investigating gilteritinib (NCT04293562), while the NOPHO-DB-SHIP consortium is enrolling children in the Quizartinib trial (EU CT 2023-505000-27-01), linked to the Master of CHIP-AML22 (EU CT 2023-504999-25-00).

There is a large number of other promising new agents for children with R/R AML, such as antibody-drug conjugates, bispecific antibodies, IDH1/2 inhibitors, inhibitors of MDM2 and MDMX proteins, and inhibitors of nuclear export, such as selinexor. Finally, there is the development of cellular therapies, already successful in acute lymphoblastic leukemia.[5]

It is very likely that all these innovations in the treatment of refractory and relapsed AML in children and adolescents will result in higher survival rates. Apart from survival, quality of life on the short- and long-term will also become a more and more important end-point. Hopefully, more effective and less toxic novel treatments will allow using less of the toxic old-fashioned chemotherapy. Ideally, even making it possible to omit allogeneic stem cell transplantation (allo-SCT), at least in some patients. After all, allo-SCT is associated with significant morbidity and late effects, and even mortality. Perhaps very sensitive techniques measuring the level of molecular residual disease pre- and post-SCT will be helpful in this context.[9] Meanwhile, allo-SCT is standard-of-care for refractory and relapsed AML, even if that would concern a second transplant, and outcomes in that setting are improving.[10] Ultimately, we should avoid refractory and relapsed disease, and therefore it is important to quickly move novel agents and novel treatment modalities to clinical trials in newly diagnosed AML. In trying to further improve outcome of pediatric AML, we should not forget that the far majority of children with AML is diagnosed in low- and middle income countries. Efforts to develop less toxic and affordable regimen that can be applied in resource-limited settings is therefore very important as well.

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